CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ISAZOPHOS

Chemical Code # 2282, Tolerance # 51554
SB 950 # not assigned

6/15/88 (original)
7/21/92 (revised)

I. DATA GAP STATUS

Combined, rat:	No data gap, **possible adverse effect**
Combined, mouse:	Supplemental data; no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, **possible adverse developmental effect**
Teratology, rat:	Data gap, **possible adverse developmental effect indicated**
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome mutation:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold faced volume and record numbers indicate a possible adverse effect.
File name: T920721

These pages contain summaries only. Individual worksheets may contain additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

Combined, Rat

021 062826 "Two-year chronic oral toxicity study with CGA-12223 technical in albino rats" (IBT, No. 8532-10607, 8/27/82). Isazophos, tech. administered in diets of CD* rats (60/sex/group designated for lifetime study, additional 5/sex/group for 12-month interim sacrifice and 5/sex/group for recovery study) at 0, 0.2, 1.0, 20, and 200 ppm (nominal). The apparent cholinesterase (ChE) inhibition NOEL was 1.0 ppm (based on inhibition of RBC and plasma ChE at higher doses in M and F). There was moderate but consistent brain ChE inhibition in 200 ppm females. There were no associated clinical signs. No evaluation of non-ChE-inhibition NOEL was attempted in this review, however 200 ppm was apparently only moderately toxic. The high dose appeared to slightly reduce body weights of females throughout the study. There was **little or no strong and consistent evidence of treatment effects**. **NOT ACCEPTABLE, not upgradeable:** (EPA has classified study as "Core Supplementary Data", hence study does not fill data requirements). (C. Aldous, 5/19/88).
DISCUSSION: This IBT study was initiated 4/6/77, and was apparently only a few months underway when serious management problems at IBT were identified. Clearly, significant efforts had been made to preserve the study from that time forth. Ciba-Geigy's own audit identified a variety of discrepancies, largely reconcilable. EPA validated the study on 12/22/83, and classified it as "Core Supplementary Data" on 1/30/84. CDFA is unaware that this study has subsequently been upgraded by EPA to a classification which could fill a data requirement. In the absence of an EPA upgrade, there is no justification for CDFA to expend further resources on behalf of this study.

029 063052 "One-Year Interim Report: Lifetime Dietary Oncogenicity and Chronic Toxicity Study in Albino Rats with CGA-12223." (Hazleton Laboratories America, WI, 6/19/86, Study No. 6117-113) CGA 12223, technical, no purity stated; fed in the diet to 90/sex in control and high dose group and 80/sex in low- and mid-dose groups; fed at 0, 0.1, 1 or 300 ppm - dose reduced for females to 250 ppm at week 22 because of excessive body weight depression (>20%) and clinical signs; 8 or 10/sex sacrificed at week 52 and 10/sex sacrificed after a 4 week recovery period; remainder of survivors continued on study; plasma and red blood cell cholinesterases inhibited in high dose group with females showing a greater depression in activity than males; clinical signs of tremors, excessive salivation, anorexia, urine staining and sensitivity to touch noted in high dose females; no histopathological findings reported in interim sacrifice; **NO ADVERSE EFFECTS indicated**, **UNACCEPTABLE** (no purity stated, no analysis of diets, interim report). (Gee, 5/23/88).

** **050 68792**, "Lifetime Dietary Oncogenicity and Chronic Toxicity Study in Albino Rats with CGA-12223", (Hazleton Laboratories America, Inc., Madison, WI, Laboratory, Study No. HLA 6117-113, 12/14/87), CGA-12223 Technical (94.9% purity, FL No. 840843, HLA sample no. 40502479); 80 Crl:CD*(SD)BR rats/sex/ dose; 0 (diet), 0.1, 1.0, or 300 ppm for 24 months; additional 10 rats/sex included in the control and high dose groups to assess recovery after 12 months of exposure; dose level for high dose females was changed to 250 ppm beginning week 22, then to 200 ppm beginning week 66 due to excessive mortality (24%); RBC, plasma, and brain cholinesterase activities inhibited up to 38, 77, and 13% as compared to control values, respectively, ($p<0.05$) in high dose females at 12 and 24 months; similar results were reported in high dose males except that brain cholinesterase was unaffected; **POSSIBLE ADVERSE EFFECTS**: high dose animals exhibited tremors; other clinical symptoms associated with cholinesterase inhibition included excessive salivation,

rhinorrhea and urine staining; no evidence of oncogenic potential; NOEL (M/F) = 1 ppm (cholinesterase inhibition, tremors, and reduced body weight); **acceptable**; (DiBiasio and Leung, 6/1/92; revised, Leung and Patterson, 7/20/92).

Combined, Mouse

051 68793, "Lifetime Dietary Oncogenicity and Chronic Toxicity Study in Albino Mice with CGA-12223", (Hazleton Laboratories America, Inc., Madison, WI, Laboratory Study No. HLA 6117-112, 1/5/88), CGA-12223 Technical 94.9% purity, FL No. 840843, HLA sample no. 40502479, light brown liquid administered in the diet to 110 (control and high dose) or 100 (other dose levels) 5 week old Crl:CD*-1(ICR)BR mice/sex at 0 (Rodent Chow), 0.3, 1.0, 30, or 300 ppm; study terminated after 8 weeks due to numerous unscheduled deaths and moribund animals with no apparent cause of death; deaths and moribund sacrifices from control to high dose, respectively, were males: 0/110, 2/100, 1/100, 1/100, 15/110, and females: 3/110, 3/100, 4/100, 2/100, 9/110; no dose-related abnormalities in the 10 mice/sex/dose that were necropsied and examined histopathologically or in animals that died or were sacrificed prior to termination; clinical signs observed only in high dose animals and included unscheduled deaths, swollen and urine stained genitals, hunched posture, thin body, rough hair coat; reduced body weights and food consumption in high dose males and females throughout study; decreased brain cholinesterase activity in both sexes at 30 and 300 ppm (males: 90% and 66% of control, $p<0.05$, respectively; females: 82% and 64% of control, $p<0.05$, respectively); **Supplemental Study.** (DiBiasio and Leung, 7/10/92)

Chronic Toxicity, Dog

013 061988, "Six month (26 week) subchronic toxicity study of CGA-12223 in beagle dogs". Food and Drug Research Laboratories (FDRL), 2/15/83. CGA-12223 Technical (93.8%) = Isazophos. Beagle dogs used in the primary 6-month study had been previously treated with up to 200 ppm in diet or 8.63 mg/kg by capsule for 4 weeks, then taken off treatment for 4 weeks, prior to being placed on a less rigorous dosing regimen for the 6-month study (See summary of preliminary study, 017:62287, in background section of review worksheet). Initial dosages for the 6-month study were 0, 0.05, 0.3, and 100 ppm (high dose reduced to 20 ppm on day 15) as dietary supplement. **NO ADVERSE EFFECTS** indicated**.** No ChE NOEL (plasma ChE apparently depressed at all doses in males and possibly females down to the lowest dosage of 0.05 ppm). NOEL (exclusive of ChE inhibition) = 20 ppm (slight, apparently transient decrease in food consumption (M and F); occasional slight tremors in one 100 ppm female). No adverse effects indicated. **UNACCEPTABLE**, **not upgradeable** (dosage range too low to characterize chronic or subchronic effects). (C. Aldous, 5/12/88)

51554-017 062822 Same record as 017:062287, cited in 1-liner for 013:061988, above.

047; 68789; "Chronic Toxicity Study in Dogs with CGA-12223 Tech." (Pharmaceuticals Division, Ciba-Geigy Corp, Summit, NJ, Study No. 852023, Toxicology/Pathology report no. 87042, 1/21/88). CGA-12223 Technical (94.9% purity, Batch FL 840843); 0 (diet), 0.05, 0.15, 2.0 and 50 ppm (not corrected for purity); 4 beagles/sex/dose for 60 weeks; no treatment-related clinical signs or mortalities reported with the exception of one male in the 2 ppm group which died during week 60; cause of death not established; **NO ADVERSE EFFECTS; reduction in serum (16.6% - 73.6% of control, $p<0.01$) and RBC (56.6% - 81.4% of control, $p<0.01$) cholinesterase activities at concentrations $\geq$ 2 ppm without any clinical signs; brain cholinesterase activity was unaffected; no treatment-related changes in urinalysis, organ weights, gross and

microscopic pathology; NOEL(M/F) = 0.15 ppm (decreased cholinesterase activity); **acceptable**; (DiBiasio and Leung, 11/22/91; revised, Leung and Patterson, 7/20/92)

Oncogenicity, Mouse

021 062825 "Carcinogenicity evaluation with CGA-12223 technical in albino mice". IBT, No. 8532-07921, 7/30/82. Isazophos, tech. administered in diets of CD-1 mice (50/sex/group) at 0, 0.2, 100, and 300 ppm (nominal). Apparent NOEL = 0.2 ppm nominal (which diets assayed to 10 ppm TWA during the last 5 months of the study), based on hemosiderin-laden macrophages in spleens of F at 100 and 300 ppm and of M at 300 ppm. Possible treatment toxicity to adrenal glands (M and F) and toxicity or pre-disposition to disease in lungs in M and F at 300 ppm. Decreased M body weight at 300 ppm. **POSSIBLE ADVERSE EFFECT**: mammary gland adenocarcinoma in 300 ppm F. **NOT ACCEPTABLE, not upgradeable:** (multiple deficiencies in design and conduct of this IBT study). (C. Aldous, 5/16/88).
EPA classification of this IBT study: "INVALID".

** 048 68790, "Oncogenicity Study in Mice of CGA-12223 Technical", (Hazleton Laboratories America, Inc., Madison, WI, Lab. Study No. HLA 6117-114, 12/14/87), CGA-12223 Technical (94.9% purity, FL No. 840843, HLA sample no. 40502479); 60 Crl:CD-1*(ICR)BR mice/sex; 0 (diet) 0.3, 1.0, 30, or 300 ppm for 18 months, except high dose males were terminated at week 65 because of low survival; an additional 10/sex were included in the control and high dose groups to assess recovery after 12 months of exposure; excessive mortalities at 300 ppm prompted a reduction in dosage to 250 ppm beginning week 23; **no adverse effects**; RBC, plasma, and brain cholinesterase activities inhibited up to 67%, 84%, and 25% as compared to control values, respectively, ($p<0.05$) in both sexes from the highest dose at 12 and 18 months; similar inhibition of cholinesterase was reported in females treated at 30 ppm; males from the same dose group did not demonstrate any inhibition of brain cholinesterase; clinical signs including tremors and convulsions occurred without any differences in frequency between control and treated animals; urine stains in the genital area were observed more frequently in males exposed to 300/250 ppm; no evidence of compound-related oncogenicity; NOEL (M/F) = 1.0 ppm (decreased cholinesterase activities). **Acceptable.** (DiBiasio and Leung, 6/5/92; revised, Leung and Patterson, 7/13/92)

Reproduction, Rat

020 62824, "Three-Generation Reproduction Study with CGA-12223 Technical in Albino Rats", (Industrial Bio-Test Laboratories, Inc., # 623-07922, 7/30/82), CGA-12223 Technical, no purity stated, administered in the diet at 0, 0.2, 1.0, and 20.0 ppm for 3 generations with 2 litters/generation and with 8 males and 16 females/group. **NO ADVERSE EFFECTS** reported. **INVALID STUDY**. (Gee 5/11/88)

006 63086, "Reproduction Study - Techn. CGA 12223, Rat, Segment II (Test for teratogenic or embryotoxic effects)", (Ciba-Geigy Ltd., experiment # 227429, 9/5/74), CGA-12223 technical, batch P.3., purity and stability not provided, administered by gavage on days 6-15 of pregnancy at 0 (2% CMC), 1, 3, and 6 mg/kg with 18 to 27 pregnant Sprague-Dawley females/group. Reduced feed consumption, decreased maternal bodyweight gain, and 5/25 maternal deaths were reported at 6 mg/kg. For fetuses, 1/3 for visceral and 2/3 for skeletal exams. **NO ADVERSE DEVELOPMENTAL EFFECTS** reported. NOEL (maternal) = 3 mg/kg, (developmental) $\geq$ 6 mg/kg. **UNACCEPTABLE** (summary report only), **might be upgraded** with submission of full report. (Gee 5/17/88)

**** 049; 068791**; "Two-Generation Reproduction Study in Rats" (Hazleton Laboratories America, Inc, Vienna, VA, Study No. 483-236, 3/3/88); CGA-12223 Technical (Lot No. FL841067, 93% purity); 0 (diet), 0.1, 1.0, 25, or 125 ppm in the diet to 30 Sprague-Dawley rats/sex/dose; parental males and females from F0 and F1 generations treated at 125 ppm had their plasma, RBC, and brain cholinesterase activities inhibited up to 98%, 95%, and 84%, as compared to control values, respectively, ($p<0.05$); similar results were reported in 25 ppm-treated parental animals with the exception that brain cholinesterase activities were unaffected in F0 and F1 females; **possible adverse develop- mental effects**: decreased pup viability and mean pup weight at 125 ppm; Reproductive NOEL = 25 ppm (postnatal growth retardation and mortality); Parental NOEL = 1.0 ppm (Decreased cholinesterase activities) **Acceptable.** (DiBiasio and Leung, 6/8/92; revised, Leung and Patterson, 7/21/92).

Teratology, Rat

012, 014, 067; **062658, 062097, 095170**; "A Teratology Study of CGA-12223 Technical in Rats." (Science Applications, Inc., La Jolla, CA, Study No. 282012, 2/25/83) CGA 12223 technical, lot FL-811181, 93.8%, amber liquid given by oral gavage to 30 female Sim:(SD)fBR rats/dose on days 6 - 15 of gestation at 0 (0.2% CMC), 1, 3, or 6 mg/kg in phase I and at 0 or 12 (reduced to 9 after 3 - 5 days of dosing) mg/kg in phase II. Second phase was initiated because of lack of signs in phase I up to 6 mg/kg. Mortalities: 4/30 dams at 9 mg/kg. **Adverse developmental effects:** early embryonic death. Maternal NOEL = 6 mg/kg (mortality, tremors, hypoactivity, discharge from vagina, mouth, nose, and eyes, anal staining, diarrhea, and decreased weight gain), Developmental NOEL = 3 mg/kg (rudimentary ribs, 14), Developmental NOAEL = 6 mg/kg (increased resorbed fetuses, decreased fetal body weight, rudimentary ribs, 14). Originally reviewed as **unacceptable** (no analysis of dosing solutions for actual content - samples were sent to sponsor), upgradable (Gee, 5/20/88). Rereviewed after submission of analysis of phase I dosing solutions. Status remains **unacceptable** (no analysis of phase II dosing solutions and up to 33% difference between actual and theoretical compound content of phase I dosing solutions), **may be upgradeable**. (DiBiasio and Gee, 9/12/91)

006 63086, "Reproduction Study - Techn. CGA 12223, Rat, Segment II (Test for teratogenic or embryotoxic effects)", (Ciba-Geigy Ltd., experiment # 227429, 9/5/74), CGA-12223 technical, batch P.3., purity and stability not provided, administered by gavage on days 6-15 of pregnancy at 0 (2% CMC), 1, 3, and 6 mg/kg with 18 to 27 pregnant Sprague-Dawley females/group. Reduced feed consumption, decreased maternal bodyweight gain, and 5/25 maternal deaths were reported at 6 mg/kg. For fetuses, 1/3 for visceral and 2/3 for skeletal exams. **NO ADVERSE DEVELOPMENTAL EFFECTS** reported. NOEL (maternal) = 3 mg/kg, (developmental) $\geq$ 6 mg/kg. **UNACCEPTABLE** (summary report only), **might be upgraded** with submission of full report. (Gee 5/17/88)

Teratology, Rabbit

006 63087, "Report on CGA 12223 tech. Teratology Study (seg. II) in Rabbits", (Ciba-Geigy Ltd., Sisseln, Switzerland, test # 79 1790, 11/22/80), CGA 12223 technical, batch op 68, 95.4% purity, administered in CMC by gavage on days 6-18 of pregnancy at 0, 1, 3, and 6 mg/kg with 20 mated female Chinchilla rabbits/group. **NO ADVERSE EFFECTS** reported. NOEL maternal $\geq$ 6 mg/kg, developmental $\geq$ 6 mg/kg. **UNACCEPTABLE,** (MTD was not demonstrated with no justification of selection, no analysis of dosing solutions). (Gee 5/12/88)

** 006 067 63088 95170 , "Rabbit Teratogenicity Study (Combined Range Finding and Definitive Study)", (Stillmeadow, Inc., project # 2324-81, 1/4/82), CGA 12223 technical, FL-811181, 93.8% purity, range-finding portion was conducted by 6 hour daily administration of undiluted test article for 2to 13 days to clipped, intact skin at 50, 75, 100, 200, 250, or 500 mg/kg with 2 or 5 unmated females/group. The teratology portion consisted of 6 hour daily exposure on gestation days 7 through 19 to clipped, intact skin with 2% CMC as vehicle at 0, 5, and 50 mg/kg and undiluted test material at 50, 75, and 150 mg/kg with 18 or 19 mated females/group. Muscle tremors and decreased activity were noted beginning at 5 mg/kg with the number of animals/group effected increasing with dose level. (# maternal deaths/# dosed)/dose level: with CMC = (3/18)/50 mg/kg; undiluted = (2/19)/50 mg/kg, (4/18)/75 mg/kg, and (13/18)/150 mg/kg. **NO ADVERSE EFFECTS** reported. NOEL (maternal) < 5 mg/kg (muscle tremors and decreased activity), developmental NOEL = 75 mg/kg (reduced mean fetal bodyweights). Originally reviewed as **UNACCEPTABLE, UPGRADEABLE** with submission of justification of route (Gee 5/16/88). Rereviewed after submission of justification of route, status changed to **ACCEPTABLE.** (DiBiasio and Gee, 9/25/91).

Mutagenicity, Gene Mutation

006 063091 "Salmonella/Mammalian-Microsome Mutagenicity Test with CGA 12 223 (Test for mutagenic properties in bacteria." (Ciba-Geigy, Basle, 12/11/80), CGA 12 223, Drum 20, batch 11 + 12, no purity stated; tested by plate incorporation with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without rat liver activation, triplicate plates, single trial; concentrations of 0, 25, 75, 225, 675 and 2025 µg/0.1 ml/plate; mean plate count reported with no standard deviation; **UNACCEPTABLE** (no purity statement, no individual plate counts, no justification of high concentration with no evidence of cytotoxicity). **Not upgradable**. (Gee, 5/9/88).

030 063137 "Point Mutation Assay with Mouse Lymphoma Cells Host-Mediated Assay with CGA 12223 (Test for mutagenic properties in mammalian cells.)" (Ciba-Geigy, Basle, 12/2/82) CGA 12223, Op. 68, 95.4% technical; mouse lymphoma cells, L5178Y, were injected into the peritoneal cavity of 4 mice/group at 106 per mouse; three days later, test material was given orally at 0 (vehicle) or 12.0 mg/kg; three days later, cells were harvested from the peritoneal cavity, viability determined and cells tested for mutagenicity to resistance to methotrexate, thymidine and cytosine arabinoside; number of cultures not given; no data on viability in mutagenicity test; preliminary test indicated a 29% reduction in cells at doses of 12.0 mg/kg; **no indication of increase in mutation frequency** in the host-mediated assay as conducted; **UNACCEPTABLE** (inadequate presentation of data with no viability, no colony counts, number of tubes not given, no individual data.) (Gee, 5/18/88).

** 030 063138 "Salmonella/Mammalian-Microsome Mutagenicity Test." (Ciba-Geigy, Basle, 11/24/86) CGA12223, technical, 94.2%, FL 841067; tested in Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without Aroclor-induced rat liver activation, in triplicate, two trials, at 0, 20, 78, 313, 1250 and 5000 µg/plate; precipitate in soft agar at 1250 and 5000 µg/plate, no cytotoxicity; **no increase in reversion rate**; **ACCEPTABLE.** (Gee, 5/18/88).

Mutagenicity, Chromosome

006 063092 "Dominant Lethal Study on CGA 12223 Technical - Mouse (Test for cytotoxic or mutagenic effects on male germinal cells)." (Ciba-Geigy,

Basle, 8/4/76) CGA 12223, no purity stated; given in a single oral gavage at 0, 4 or 12 mg/kg to 20 male NMRI-derived mice per group; mated 1 male: 2 females for 6 weekly periods; **no evidence of a dominant lethal effect**; **UNACCEPTABLE** (no justification of dose selection, no individual data, no purity of test material, no concurrent or historical control data.) (Gee, 5/9/88).

030 063133 "Nucleus Anomaly Test in Somatic Interphase Nuclei - CGA 12223 - Chinese Hamster (Test for mutagenic effects on bone marrow cells)", (Ciba-Geigy, Basle, 8/24/81) CGA12223, batch Op.68, 95.4% technical; given by oral gavage in two daily doses to 6/sex/group at 0, 5.5, 11 or 22 mg/kg; sacrificed at 24 hours after the second dosing; scored 1000 bone marrow cells from 3/sex/group for Jolly bodies, micronuclei and polyploidy; no PCE/NCE ratio or mitotic index; 1 mid-dose and 3 high-dose animals died; **no evidence for micronuclei formation** in the assay as conducted; **UNACCEPTABLE** (single sampling time without justification, scored inadequate number of animals with no explanation for selection of those scored, no description of test material), not upgradable. (Gee, 5/13/88).

** 030 063135 "Micronucleus Test (Mouse)." (Ciba-Geigy, Basle, 11/24/86) CGA 12223, Batch FL 841067, 94.2%, given by oral gavage in a single dose at 0, 6.0 or 18.0 mg/kg, sacrificed at 24, 48 and 72 hours, 8/sex/group, positive control of cyclophosphamide at 24 hours only; **no evidence of increase in micronucleus formation** with test article, decrease in ratio of PCE/NCE at 24 hours with treatment (dose-related) in both sexes but not at 72 hours; **ACCEPTABLE**. (Gee, 5/17/88).

Mutagenicity, DNA

030, 059 063053, 069268 "Autoradiographic DNA Repair Test on Rat Hepatocytes." (Ciba-Geigy, Basle, Study No. 820197, 2/25/87), CGA 12223 technical, 93.5%, Op. 68, hepatocytes isolated from a male rat and incubated with CGA-12223 at concentrations of 0, 1, 5, 25 and 125 nl/ml, 4 cultures/concentration, incubated for 5 hrs, autoradiographic exposure 6 days, scored 50 nuclei from each of 3 slides, dimethylnitrosamine 100 µM as positive control; slides initially read with a microscope without considering incorporation into cytoplasm, slides reread with an electronic counter and cytoplasmic background subtracted; **No evidence of unscheduled DNA synthesis**; Originally reviewed by Gee, 5/23/88, report supplemental to report dated 12/9/82, unacceptable but upgradable (with submission of initial report dated 12/9/82). Rereviewed after submission of initial report. Status remains **Unacceptable** but may be upgradable with data on viability data of freshly isolated hepatocytes and subsequent viabilities during the study. (DiBiasio and Gee, 1/7/92).

030 063132 "Autoradiographic DNA Repair Test on Human Fibroblasts (In vitro test for DNA-damaging properties)" (Ciba-Geigy, Basle, 12/9/82) CGA 12223, technical, batch Op. 68, 95.4% technical; tested without activation only with human fibroblasts CRL 1121, at 0, 0.5, 2.5, 12.5 or 62.5 nl/ml, 5 hours incubation, 4 slides per concentration; scored 50 nuclei per slide for a total of 200; background from cell-free areas of slide; no inhibition of semiconservative DNA synthesis; 6-^{3}H-thymidine incorporation by autoradiography; **no evidence in the study as conducted of induced unscheduled**

DNA synthesis; **UNACCEPTABLE** (no activation, no cytotoxicity data to justify concentrations, others), **not upgradable**. (Gee, 5/12/88).

030 063134 "BALB/3T3 Cell Transformation Assay - (In vitro test for transformation-inducing properties in mammalian fibroblasts)", (Ciba-Geigy, Basle, 6/27/83), CGA 12223, batch Op. 68, 95.4% technical; mouse embryo fibroblasts BALB 3T3 clone A31-1-1, tested without activation only with 0, 0.188, 0.375, 0.750, 1.5 and 3.0 µg/ml, for 72 hours, 15 dishes per concentration; 3 dishes/concentration at 200 cells each for viability; selection of concentrations used based on toxicity test but no data presented; no evidence for cell transformation with treatment; no difference in viability between treated and control samples; **no evidence for cell transformation due to test material**; **UNACCEPTABLE** (testing of inadequate concentrations, inadequate description of study procedures) (Gee, 5/13/88).

** 030 063136 "Saccharomyces cerevisiae D7/Mammalian-Microsome Mutagenicity Test in vitro with CGA 12223 (Test for mutagenic properties in yeast cells)." (Ciba-Geigy, Basle, 12/15/82) CGA 12223, Batch Op. 68, 95.4% technical, tested with and without rat liver activation with Saccharomyces cerevisiae strain D7 at 0, 40, 200, 1000 and 5000 µg/ml, 16 hours incubation in suspension; plated 5 each with two selective media for gene conversion and mutation and 10 plates each concentration for mitotic crossing-over; two independent trials; **no evidence for any genotoxic effect** reported**; ACCEPTABLE**. (Gee, 5/17/88).

Neurotoxicity

014 062375, "42-Day Neurotoxicity Study with CGA 12223 Technical in Chickens." (IBT, no. 8580-10767, 4/19/78), CGA 12223 Technical, FL-770344, no purity stated; preliminary test with 2/group at 14.7, 21.5, 31.6, 46.4, 68.1, or 100 mg/kg by oral gavage - all birds died within 3 hours; additional trials were run to determine the LD50 of 9.03 mg/kg; in the neurotoxicity phase, 10 birds served as untreated controls, 15 as positive controls with TOCP and 40 were given 9.03 mg/kg CGA 12223 with 10 mg/kg atropine given im 1 hour before dosing; dosing repeated at 21 days with survivors without atropine or 2-Pam; signs of toxicity were lethargy, generalized weakness and ataxia; 18/40 died during the test period, primarily after the second dosing; no clinical signs of delayed neurotoxicity and no histopathological findings reported; tissues from 10 survivors with lowest animal numbers were examined as confirmed in a memo dated 9/7/77; individual data from handwritten lab notebooks with some pages not clear; Unacceptable (no purity of test material, no age or strain of birds, inadequate quality assurance of data, no analysis of dosing solutions). No evidence of delayed neurotoxicity reported. Evaluated as **"Supplementary data"** by EPA. Gee, 5/20/88.

** 015; 62376; "Acute Delayed Neurotoxicity in Domestic Fowl, CGA-12223 Tech. (93.8%), FL-811484" Project No: 3290-84; Stillmeadow, Inc., Houston, TX; 09/05/84; isazophos, 93.8% purity, 1.05 % v/v solution in corn oil; on days 0 and 21, 12 fasted hens were treated by oral gavage with 13.1 mg/kg and observed to day 42; negative and positive controls, cholinesterase protection, and histopathology were adequate; **no dose-related delayed neurotoxicity observed**; study **ACCEPTABLE** for registration of the technical active ingredient; (Morris and Patterson, 04/18/88).

51554-006; 63089; "Acute Oral LD_{50} and Neurotoxicity Study of Technical CGA 12223 in the Domestic Fowl (*Gallus domesticus*)," Project No: Siss 3651; Ciba-Geigy Limited, Basle, Switzerland; 09/11/74; isazophos, purity not stated; acute delayed neurotoxicity of CGA 12223 was assessed in 2 White Leghorn chickens / sex by dosing with 10, 27.8, or 60 mg/kg at day 0 and the survivors with

10 or 27.8 mg/kg at day 21 and observed thru day 42; **NO ADVERSE EFFECTS** reported; study was **NOT ACCEPTABLE** and **not upgradeable** because there were not enough surviving hens; an acceptable neurotoxicity study has been evaluated (see doc. # 51554-015, rec. # 62376); (Morris and Patterson, 04/19/88).

** 51554-004; 63066; Special Toxicological Study; 857; Rat; CIBA-GEIGY LIMITED, Basle, Switzerland, 4/9/75; CGA-12223 Technical (Isazophos), CGA-15324 Technical; 5/sex/dose; Acute Oral LD50: (CGA-12223) 10, 21.5, 31.7, 46.4, 60, 100 mg/kg, (CGA-15324) 215, 278, 359, 464 mg/kg; Antagonism Study: (CGA-12223 oral LD80-49 mg/kg), atropine sulfate (AS), Toxogonin (TOX) dosed separately: 5 mg/kg-(sc, im) 3 hr, 1 hr before, (ip) 10 min after, 10 mg/kg-(sc) 3 hr, 1 hr before, (im) 3 hr, 1 hr, 30 min before, (ip) 10 min after, 20 mg/kg-(im) 1 hr before; Combined dose of AS, TOX: 5 mg/kg each- (sc, im) 3 hr, 1 hr before, (ip) 10 min after, 10 mg/kg each (same as 5 mg/kg); (CGA-15324 oral LD80-430 mg/kg), AS: 5 mg/kg, (sc) 3 hr before, 3, 6 hr after, (im) 3 hr before, 3, 6 hr after, (ip) 10 min, 1 hr after, 10 mg/kg, (sc, im) 3, 6 hr after, (ip) 4 hr after, 20 mg/kg (same as 10 mg/kg); Tox: 5 mg/kg, (sc, im) 3 hr before, 3, 6, 21 hr after, (ip) 10 min, 1 hr after; 10 and 20 mg/kg, (sc, im) 3, 6 hr after, (ip) 4 hr after; Combined dose of AS, TOX: 10 mg/kg each, (sc, im) 3, 6 hr after, (ip) 4 hr after; Observations: sedation, dyspnea, exophthalmus, tonic-clonic muscle spasms; both AS, TOX separately or together improved the survival of animals treated with CGA-12223, TOX being the more effective of the two, treatment ip 10 minutes after the most effective route, neither AS or TOX antagonized the toxic effects of CGA-15324; CGA-12223 LD50 (95% confidence limits) (M/F)=33 mg/kg (25 to 42); Toxicity Category I; Study **Acceptable**. (Moore, 4/14/92).

** 51554-004; 63067; Acute Oral Toxicity, Special Toxicological Study; 811, 857; Rat; CIBA-GEIGY LIMITED, Basle, Switzerland; 10/20/76; CGA-12223 Technical (Isazophos); 5/sex/dose; Acute Oral LD50: 10, 21.5, 31.7, 46.4, 60, 100 mg/kg; Treatment regimen: (CGA-12223 oral LD96-75 mg/kg), Atropine (AS) alone, ip, sc, im, single and multiple dosing after onset of signs, 10.0, 17.4 or 20.0 mg/kg; Pralidoxime (PAM) alone, ip, im, sc; single and multiple dosing after onset of signs, 50 or 100 mg/kg; Toxogonin (TOX) alone, ip, im, single and multiple dosing after onset of signs, 10, 20, or 30 mg/kg; Multiple Regimen: AS + PAM, im, ip, single or multiple dosing after onset of signs, PAM-50 mg/kg, AS-10 or 20 mg/kg; TOX + AS, im, ip, single or multiple dosing regimens, TOX-10, 20, or 30 mg/kg, AS-10 or 20 mg/kg; PAM + AS, 5x challenging dose 33 mg/kg (LD50) CGA-12223 prior to 75 mg/kg, im, multiple dosing after onset of signs, PAM-50 mg/kg, AS-10 mg/kg; TOX + AS, 5x challenging dose 33 mg/kg (LD50) CGA-12223 prior to 75 mg/kg, im, multiple dosing after onset of signs, TOX-20 mg/kg, AS-10 mg/kg; Observations: sedation, dyspnea, exophthalmus, tonic-clonic muscle spasm; TOX + AS most effective treatment regimen; LD50 (95% confidence limit) (M/F)-33 mg/kg (25 to 42); Toxicity Category I; Study **Acceptable**. (Moore, 4/16/92)

STUDIES ON METABOLITES

CGA 17193 is 5-chloro-1-(methylethyl)-3-hydroxy-1H-1,2,4-Triazole

027 063125 "Rat Acute Oral Toxicity." (Stillmeadow, Inc., TX, 8/8/84), CGA 17193, metabolite of isazophos, no purity stated; given by oral gavage at 5030 mg/kg to 5 male and 5 female rats; observation for 14 days; no mortality; category IV. **Supplemental data**. Gee, 5/10/88.

027 063126 "28-Day Range-Finding Study in Albino Rats with CGA 17193 - Final Report." (Litton Bionetics [Hazleton], project 22310, 11/85), CGA 17193 technical, 99.3%; fed in the diet at 0, 500, 5000 or 50,000 ppm to 20/sex/group; 10/sex/group were sacrificed at 2 weeks, survivors at 4 weeks; no histopathological findings reported; decreased body weight gains at the high dose in both sexes; systemic NOEL = 5000 ppm; report states the NOEL to be 500 based on occasional variations in hematology, clinical chemistry and organ weights - significance of these is difficult to evaluate in this study; **supplemental data** on metabolite. Gee, 5/10/88.

027 063122 "Salmonella/Mammalian-Microsome Mutagenicity Assay (Ames Assay)." (Ciba-Geigy, Summit, NJ, 8/17/84, Report No. 181-84) CGA 17193, metabolite of isazophos, no purity stated; tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, with and without rat liver activation, triplicate plates, two trials; concentrations were 0, 100, 500, 2500 or 10,000 µg/plate; **no increase in reversion rate; supplemental data**. Gee, 5/9/88.

027 063123 "Mutagenicity Evaluation of CGA 17193 Technical (99.3%) FL 841296 in an in vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cell - Amended Final Report." (Litton Bionetics, amended report date 4/85), CGA 17193, technical, 99.3%; tested with and without Aroclor-induced rat liver activation at 0, 3.6, 4.2, 4.7 or 5.2 mg/ml; incubation without activation was for 17.5 hours followed by an additional 2.5 with colcemid; with activation, incubation for 2 hours with test material followed by 8.0 hours in complete medium and 2.5 with colcemid; incubation times based on preliminary study on cell cycle progression; no evidence for increase in chromosomal aberrations to concentrations which were slightly toxic and caused cycle delay; **supplemental data** on metabolite. Gee, 5/9/88.

027 063124 "Evaluation of CGA 17193 Technical in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay - Final Report." (Litton Bionetics, Project No. 20991, 4/85), CGA 17193 technical, 99.3%; tested with primary rat hepatocytes for 18 - 19 hours at 0, 50, 125, 250, 500, 1250, 2500 or 5000 µg/ml; toxic at 2500 and above; scored 50 nuclei on each of 3 coverslips; no evidence of increase in unscheduled DNA synthesis; **supplemental data** on metabolite. Gee, 5/9/88.

058 69267 "90-Day Oral Toxicity Study in Rats with CGA-17193 Technical (a Metabolite of Isazophos)", (Pharmaceuticals Division, Ciba-Geigy Corp., Summit, NJ, Study No. 862288, Toxicology/Pathology report no. 87041, 11/25/87). CGA-17193 Technical, 97.7% purity, Batch FL 860013, was administered daily in powdered rodent diet at 0, 250, 2500, 10,000, and 20,000 ppm (not corrected for percent purity) to 15 Sprague-Dawley rats/sex/dose for a 13 consecutive weeks. **NO ADVERSE EFFECTS.** In males and females, increased incidences of perineal staining and decreased urinary pH were seen at 10,000 and 20,000 ppm. Also noted at 20,000 ppm in males was reduced cumulative body weight gain, generally 86% of control levels. NOEL(M/F) = 2500 ppm (based on perineal staining and decreased urine pH). **SUPPLEMENTAL DATA ONLY.** (DiBiasio and Leung, 12/20/91)

057 68806 "Subchronic Toxicity Study with CGA-17193 Technical in Dogs (a Metabolite of Isazophos)", (Hazleton Laboratories America, Inc., Madison, WI, Study No. HLA 6117-125, 1/28/88). CGA-17193 Technical, 97.7% purity, Batch FL 860013, HLA sample no. 70302104, a fine white powder, was administered daily in canine diet at 0, 200, 2000, and 20,000 ppm (not corrected for percent purity) to 4 beagles/sex/dose for a period of at least 13 weeks. **NO ADVERSE EFFECTS.** No treatment-related changes in body and organ weights, necropsy and histopathology; NOEL(M/F) $\geq$ 20,000 ppm (no effects seen at highest dose tested); **SUPPLEMENTAL DATA;** (DiBiasio and Leung, 12/4/91)